

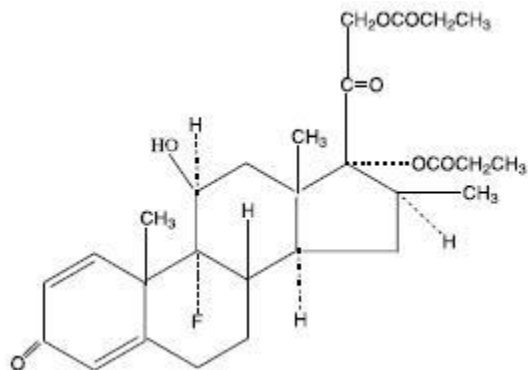
BETAMETHASONE CLOTRIMAZOLE - clotrimazole and betamethasone dipropionate cream

Stat Rx USA

DESCRIPTION

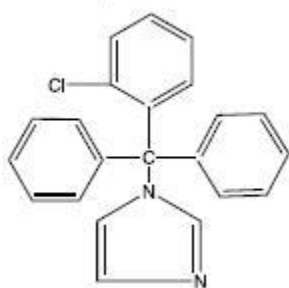
Clotrimazole and Betamethasone Dipropionate Cream USP contains a combination of clotrimazole, a synthetic antifungal agent, and betamethasone dipropionate, a synthetic corticosteroid, for dermatologic use.

Chemically, clotrimazole is 1-(*o*-Chloro- α,α -diphenylbenzyl)imidazole, with the empirical formula $C_{22}H_{17}ClN_2$, a molecular weight of 344.84, and the following structural formula:



Clotrimazole is an odorless, white crystalline powder, insoluble in water and soluble in ethanol.

Betamethasone dipropionate has the chemical name 9-Fluoro-11 β ,17,21-trihydroxy-16 β -methylpregna-1,4-diene-3,20-dione 17,21-dipropionate, with the empirical formula $C_{28}H_{37}FO_7$, a molecular weight of 504.60, and the following structural formula:



Betamethasone dipropionate is a white to creamy white, odorless crystalline powder, insoluble in water.

Each gram of Clotrimazole and Betamethasone Dipropionate Cream contains 10 mg clotrimazole and 0.64 mg betamethasone dipropionate (equivalent to 0.5 mg betamethasone), in a hydrophilic cream.

INACTIVE INGREDIENTS

Cetereath-30, cetyl alcohol, mineral oil, propylene glycol, purified water, sodium phosphate monobasic, stearyl alcohol and white petrolatum; benzyl alcohol as preservative.

Clotrimazole and betamethasone dipropionate cream is smooth, uniform, and white to off-white in color.

CLINICAL PHARMACOLOGY

Clotrimazole And Betamethasone Dipropionate

Clotrimazole and betamethasone dipropionate cream has been shown to be at least as effective as clotrimazole alone in a different cream vehicle. Use of corticosteroids in the treatment of fungal infection may lead to suppression of host inflammation leading to worsening or decreased cure rate.

Clotrimazole

Skin penetration and systemic absorption of clotrimazole following topical application of clotrimazole and betamethasone dipropionate cream have not been studied. The following information was obtained using 1% clotrimazole cream and solution formulations. Six hours after the application of radioactive clotrimazole 1% cream and 1% solution onto intact and acutely inflamed skin, the concentration of clotrimazole varied from 100 mcg/cm³ in the stratum corneum, to 0.5 to 1 mcg/cm³ in the reticular dermis, and 0.1 mcg/cm³ in the subcutis. No measurable amount of radioactivity (less than 0.001 mcg/mL) was found in the serum within 48 hours after application under occlusive dressing of 0.5 mL of the solution or 0.8 g of the cream. Only 0.5% or less of the applied radioactivity was excreted in the urine.

Microbiology

Mechanism of Action: Clotrimazole is an imidazole antifungal agent. Imidazoles inhibit 14- α -demethylation of lanosterol in fungi by binding to one of the cytochrome P-450 enzymes. This leads to the accumulation of 14- α -methylsterols and reduced concentrations of ergosterol, a sterol essential for a normal fungal cytoplasmic membrane. The methylsterols may affect the electron transport system, thereby inhibiting growth of fungi.

Activity *In Vivo*: Clotrimazole has been shown to be active against most strains of the following dermatophytes, both *in vitro* and in clinical infections as described in the INDICATIONS AND USAGE section: *Epidermophyton floccosum*, *Trichophyton mentagrophytes*, and *Trichophyton rubrum*.

Activity *In Vitro*: *In vitro*, clotrimazole has been shown to have activity against many dermatophytes, but the clinical significance of this information is unknown.

Drug Resistance: Strains of dermatophytes having a natural resistance to clotrimazole have not been reported. Resistance to azoles including clotrimazole has been reported in some *Candida* species.

No single-step or multiple-step resistance to clotrimazole has developed during successive passages of *Trichophyton mentagrophytes*.

Betamethasone Dipropionate

Betamethasone dipropionate, a corticosteroid, has been shown to have topical (dermatologic) and systemic pharmacologic and metabolic effects characteristic of this class of drugs.

Pharmacokinetics: The extent of percutaneous absorption of topical corticosteroids is determined by many factors, including the vehicle, the integrity of the epidermal barrier and the use of occlusive dressings. (See DOSAGE AND ADMINISTRATION section.) Topical corticosteroids can be absorbed from normal intact skin. Inflammation and/or other disease processes in the skin may increase percutaneous absorption of topical corticosteroids. Occlusive dressings substantially increase the percutaneous absorption of topical corticosteroids. (See DOSAGE AND ADMINISTRATION section.)

Once absorbed through the skin, the pharmacokinetics of topical corticosteroids are similar to systemically administered corticosteroids. Corticosteroids are bound to plasma proteins in varying degrees. Corticosteroids are metabolized primarily in the liver and are then excreted by the kidneys. Some of the topical corticosteroids and their metabolites are also excreted into the bile.

Studies performed with clotrimazole and betamethasone dipropionate cream indicate that this topical combination anti-fungal/corticosteroid may have vasoconstrictor potencies in a range that is comparable to high potency topical corticosteroids. Therefore use is not recommended in patients less than 17 years of age, in diaper dermatitis, and under occlusion.

CLINICAL STUDIES

In clinical studies of tinea corporis, tinea cruris, and tinea pedis, patients treated with clotrimazole and betamethasone dipropionate cream showed a better clinical response at the first return visit than patients treated with clotrimazole cream. In tinea corporis and tinea cruris, the patient returned 3 to 5 days after starting treatment, and in tinea pedis, after 1 week. Mycological cure rates observed in patients treated with clotrimazole and betamethasone dipropionate cream were as good as or better than in those patients treated with clotrimazole cream. In these same clinical studies, patients treated with clotrimazole and betamethasone dipropionate cream showed better clinical responses and mycological cure rates when compared with patients treated with betamethasone dipropionate cream.

INDICATIONS AND USAGE

Clotrimazole and betamethasone dipropionate cream is indicated in patients 17 years and older for the topical treatment of symptomatic inflammatory tinea pedis, tinea cruris and tinea corporis due to *Epidermophyton floccosum*, *Trichophyton mentagrophytes*, and *Trichophyton rubrum*. Effective treatment without the risks associated with topical corticosteroid use may be obtained using a topical antifungal agent that does not contain a corticosteroid, especially for noninflammatory tinea infections. The efficacy of clotrimazole and betamethasone dipropionate cream for the treatment of infections caused by zoophilic dermatophytes (e.g., *Microsporum canis*) has not been established. Several cases of treatment failure of clotrimazole and betamethasone dipropionate cream in the treatment of infections caused by *Microsporum canis* have been reported.

CONTRAINDICATIONS

Clotrimazole and betamethasone dipropionate cream is contraindicated in patients who are sensitive to clotrimazole, betamethasone dipropionate, other corticosteroids or imidazoles, or to any ingredient in these preparations.

PRECAUTIONS General

Systemic absorption of topical corticosteroids can produce reversible hypothalamic-pituitary-adrenal (HPA) axis suppression with the potential for glucocorticosteroid insufficiency after withdrawal of treatment. Manifestations of Cushing's syndrome, hyperglycemia, and glucosuria can also be produced in some patients by systemic absorption of topical corticosteroids while on treatment.

Conditions which augment systemic absorption include use over large surface areas, prolonged use, and use under occlusive dressings.

Use of more than one corticosteroid-containing product at the same time may increase total systemic glucocorticoid exposure.

Patients applying clotrimazole and betamethasone dipropionate cream to a large surface area or to areas under occlusion should be evaluated periodically for evidence of HPA-axis suppression. This may be done by using the ACTH stimulation, morning plasma cortisol, and urinary free cortisol tests.

If HPA-axis suppression is noted, an attempt should be made to withdraw the drug, to reduce the frequency of application, or to substitute a less potent corticosteroid. Recovery of HPA-axis function is generally prompt upon discontinuation of topical corticosteroids. Infrequently, signs and symptoms of glucocorticosteroid insufficiency may occur, requiring supplemental systemic corticosteroids.

In a small study, clotrimazole and betamethasone dipropionate cream was applied using large dosages, 7 g daily for 14 days (BID) to the crural area of normal adult subjects. Three of the eight normal subjects on whom clotrimazole and betamethasone dipropionate cream was applied exhibited low morning plasma cortisol levels during treatment. One of these subjects had an abnormal Cortrosyn test. The effect on morning plasma cortisol was transient and subjects recovered one week after discontinuing dosing. In addition, two separate studies in pediatric patients demonstrated adrenal suppression as determined by cosyntropin testing. (See PRECAUTIONS–Pediatric Use section.)

Pediatric patients may be more susceptible to systemic toxicity from equivalent doses due to their larger skin surface to body mass ratios. (See PRECAUTIONS – Pediatric Use section.)

If irritation develops, clotrimazole and betamethasone dipropionate cream should be discontinued and appropriate therapy instituted.

THE SAFETY OF CLOTRIMAZOLE AND BETAMETHASONE DIPROPIONATE CREAM HAS NOT BEEN DEMONSTRATED IN THE TREATMENT OF DIAPER DERMATITIS. ADVERSE EVENTS CONSISTENT WITH CORTICOSTEROID USE HAVE BEEN OBSERVED IN PATIENTS TREATED WITH CLOTRIMAZOLE AND BETAMETHASONE DIPROPIONATE CREAM FOR DIAPER DERMATITIS. THE USE OF CLOTRIMAZOLE AND BETAMETHASONE DIPROPIONATE CREAM IN THE TREATMENT OF DIAPER DERMATITIS IS NOT RECOMMENDED.

ADVERSE REACTIONS

Adverse reactions reported for clotrimazole and betamethasone dipropionate cream in clinical trials were paresthesia in 1.9% of patients, and rash, edema, and secondary infection, each in 1% of patients.

The following local adverse reactions have been reported with topical corticosteroids and may occur more frequently with the use of occlusive dressings. These reactions are listed in an approximate decreasing order of occurrence: itching, irritation, dryness, folliculitis, hypertrichosis, acneiform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis, maceration of the skin, secondary infection, skin atrophy, striae, and miliaria. In the pediatric population, reported adverse events for clotrimazole and betamethasone dipropionate cream include growth retardation, benign intracranial hypertension, Cushing's syndrome (HPA-axis suppression), and local cutaneous reactions, including skin atrophy.

Systemic absorption of topical corticosteroids has produced reversible hypothalamic-pituitary-adrenal (HPA) axis suppression, manifestations of Cushing's syndrome, hyperglycemia, and glucosuria in some patients.

Adverse reactions reported with the use of clotrimazole are as follows: erythema, stinging, blistering, peeling, edema, pruritus, urticaria and general irritation of the skin.

OVERDOSAGE

Amounts greater than 45 g/week of clotrimazole and betamethasone dipropionate cream should not be used. Acute overdosage with topical application of clotrimazole and betamethasone dipropionate cream is unlikely and would not be expected to lead to life-threatening situation. Clotrimazole and betamethasone dipropionate cream should not be used for longer than the prescribed time period.

Topically applied corticosteroids, such as the one contained in clotrimazole and betamethasone dipropionate cream, can be absorbed in sufficient amounts to produce systemic effects (see PRECAUTIONS section).

DOSAGE AND ADMINISTRATION

Gently massage sufficient clotrimazole and betamethasone dipropionate cream into the affected skin areas twice a day, in the morning and evening.

Clotrimazole and betamethasone dipropionate cream should not be used longer than 2 weeks in the treatment of tinea corporis or tinea cruris, and amounts greater than 45 g per week of clotrimazole and betamethasone dipropionate cream should not be used. If a patient with tinea corporis or tinea cruris shows no clinical improvement after one week of treatment with clotrimazole and betamethasone dipropionate cream, the diagnosis should be reviewed.

Clotrimazole and betamethasone dipropionate cream should not be used longer than 4 weeks in the treatment of tinea pedis, and amounts greater than 45 g per week of clotrimazole and betamethasone dipropionate cream should not be used. If a patient with tinea pedis shows no clinical improvement after 2 weeks of treatment with clotrimazole and betamethasone dipropionate cream, the diagnosis should be reviewed.

Clotrimazole and betamethasone dipropionate cream should not be used with occlusive dressings.

HOW SUPPLIED

Clotrimazole and Betamethasone Dipropionate Cream USP is supplied in 15-gram and 45-gram tubes; boxes of one.

Store between 2°C and 30°C (36°F and 86°F).

Manufactured by

Actavis Mid Atlantic LLC

1877 Kawai Road

Lincolnton, NC 28092 USA

FORM NO. 0379

Rev. 5/06

VC2842

Information for Patients

Patients using clotrimazole and betamethasone dipropionate cream should receive the following information and instructions:

1. The medication is to be used as directed by the physician and is not recommended for use longer than the prescribed time period. It is for external use only. Avoid contact with the eyes, mouth, or intravaginally.
2. This medication is to be used for the full prescribed treatment time, even though the symptoms may have improved. Notify the physician if there is no improvement after 1 week of treatment for tinea cruris or tinea corporis, or after 2 weeks for tinea pedis.
3. This medication should only be used for the disorder for which it was prescribed.
4. Other corticosteroid-containing products should not be used with clotrimazole and betamethasone dipropionate without first talking with your physician.
5. The treated skin area should not be bandaged, covered, or wrapped so as to be occluded. (See DOSAGE AND ADMINISTRATION section.)
6. Any signs of local adverse reactions should be reported to your physician.
7. Patients should avoid sources of infection or reinfection.
8. When using clotrimazole and betamethasone dipropionate cream in the groin area, patients should use the medication for two weeks only, and apply the cream sparingly. Patients should wear loose-fitting clothing. Notify the physician if the condition persists after 2 weeks.
9. The safety of clotrimazole and betamethasone dipropionate cream has not been demonstrated in the treatment of diaper dermatitis. Adverse events consistent with corticosteroid use have been observed in patients treated with clotrimazole and betamethasone dipropionate cream for diaper dermatitis. The use of clotrimazole and betamethasone dipropionate cream in the treatment of diaper dermatitis is not recommended.

Laboratory Tests

If there is a lack of response to clotrimazole and betamethasone dipropionate cream, appropriate confirmation of the diagnosis, including possible mycological studies, is indicated before instituting another course of therapy. The following tests may be helpful in evaluating HPA-axis suppression due to the corticosteroid components:

Urinary free cortisol test

Morning plasma cortisol test

ACTH (cosyntropin) stimulation test

Carcinogenesis, Mutagenesis, Impairment of Fertility

There are no adequate laboratory animal studies with either the combination of clotrimazole and betamethasone dipropionate or with either component individually to evaluate carcinogenesis.

Betamethasone was negative in the bacterial mutagenicity assay (*Salmonella typhimurium* and *Escherichia coli*), and in the mammalian cell mutagenicity assay (CHO/HGPRT). It was positive in the *in vitro* human lymphocyte chromosome aberration assay, and equivocal in the *in vivo* mouse bone marrow micronucleus assay. This pattern of response is similar to that of dexamethasone and hydrocortisone.

Reproductive studies with betamethasone dipropionate carried out in rabbits at doses of 1.0 mg/kg by the intramuscular route and in mice up to 33 mg/kg by the intramuscular route indicated no impairment of fertility except for dose-related increases in fetal resorption rates in both species. These doses are approximately 5- and 38-fold the maximum human dose based on body surface areas, respectively.

In a combined study of the effects of clotrimazole on fertility, teratogenicity, and postnatal development, male and female rats were dosed orally (diet admixture) with levels of 5, 10, 25, or 50 mg/kg/day (approximately 1-8 times the maximum dose in a 60 kg adult based on body surface area) from 10 weeks prior to mating until 4 weeks postpartum. No adverse effects on the duration of estrous cycle, fertility, or duration of pregnancy were noted.

Pregnancy/Teratogenic Effects

Pregnancy Category C: There have been no teratogenic studies performed in animals or humans with the combination of clotrimazole and betamethasone dipropionate. Corticosteroids are generally teratogenic in laboratory animals when administered at relatively low dosage levels.

Studies in pregnant rats with intravaginal doses up to 100 mg/kg (15 times the maximum human dose) revealed no evidence of fetotoxicity due to clotrimazole exposure.

No increase in fetal malformations was noted in pregnant rats receiving oral (gastric tube) clotrimazole doses up to 100 mg/kg/day during gestation days 6-15. However, clotrimazole dosed at 100 mg/kg/day was embryotoxic (increased resorptions), fetotoxic (reduced fetal weights) and maternally toxic (reduced body weight gain) to rats. Clotrimazole dosed at 200 mg/kg/day (30 times the maximum human dose) was maternally lethal, and therefore fetuses were not evaluated in this group. Also in this study, doses up to 50 mg/kg/day (8 times the maximum human dose) had no adverse effects on dams or fetuses. However, in the combined fertility,

teratogenicity, and postnatal development study described above, 50 mg/kg clotrimazole, was associated with reduced maternal weight gain and reduced numbers of offspring reared to 4 weeks.

Oral clotrimazole doses of 25, 50, 100, and 200 mg/kg/day (2-15 times the maximum human dose) were not teratogenic in mice. No evidence of maternal toxicity or embryotoxicity was seen in pregnant rabbits dosed orally with 60, 120, or 180 mg/kg/day (18-55 times the maximum human dose).

Betamethasone dipropionate has been shown to be teratogenic in rabbits when given by the intramuscular route at doses of 0.05 mg/kg. This dose is approximately one-fifth the maximum human dose. The abnormalities observed included umbilical hernias, cephalocele and cleft palates. Betamethasone dipropionate has not been tested for teratogenic potential by the dermal route of administration. Some corticosteroids have been shown to be teratogenic after dermal application to laboratory animals.

There are no adequate and well-controlled studies in pregnant women of the teratogenic effects of topically applied corticosteroids. Therefore, clotrimazole and betamethasone dipropionate cream should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

Systemically administered corticosteroids appear in human milk and could suppress growth, interfere with endogenous corticosteroids production, or cause other untoward effects. It is not known whether topical administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in human milk. Because many drugs are excreted in human milk, caution should be exercised when clotrimazole and betamethasone dipropionate cream is administered to a nursing woman.

Pediatric Use

Adverse events consistent with corticosteroid use have been observed in patients under 12 years of age treated with clotrimazole and betamethasone dipropionate cream. In open-label studies, 17 of 43 (39.5%) evaluable pediatric patients (aged 12 to 16 years old) using clotrimazole and betamethasone dipropionate cream for treatment of tinea pedis demonstrated adrenal suppression as determined by cosyntropin testing. In another open-label study, 8 of 17 (47.1%) evaluable pediatric patients (aged 12 to 16 years old) using clotrimazole and betamethasone dipropionate cream for treatment of tinea cruris demonstrated adrenal suppression as determined by cosyntropin testing. **THE USE OF CLOTRIMAZOLE AND BETAMETHASONE DIPROPIONATE CREAM IN THE TREATMENT OF PATIENTS UNDER 17 YEARS OF AGE OR PATIENTS WITH DIAPER DERMATITIS IS NOT RECOMMENDED.**

Because of higher ratio of skin surface area to body mass, pediatric patients under the age of 12 years are at a higher risk with clotrimazole and betamethasone dipropionate cream. The studies described above suggest that pediatric patients under the age of 17 years may also have this risk. They are at increased risk of developing Cushing's syndrome while on treatment and adrenal insufficiency after withdrawal of treatment. Adverse effects, including striae and growth retardation, have been reported with inappropriate use of clotrimazole and betamethasone dipropionate cream in infants and children (see PRECAUTIONS and ADVERSE REACTIONS sections).

Hypothalamic-pituitary-adrenal (HPA) axis suppression, Cushing's syndrome, linear growth retardation, delayed weight gain and intracranial hypertension have been reported in children receiving topical corticosteroids. Manifestations of adrenal suppression in children include low plasma cortisol levels and absence of response to ACTH stimulation. Manifestations of intracranial hypertension include bulging fontanelles, headaches, and bilateral papilledema.

Geriatric Use

Clinical studies of clotrimazole and betamethasone dipropionate cream did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Post-market adverse events reporting for clotrimazole and betamethasone dipropionate cream in patients aged 65 and above includes reports of skin atrophy and rare reports of skin ulceration. Caution should be exercised with the use of these corticosteroid containing topical products on thinning skin. **THE USE OF CLOTRIMAZOLE AND BETAMETHASONE DIPROPIONATE CREAM UNDER OCCLUSION, SUCH AS IN DIAPER DERMATITIS, IS NOT RECOMMENDED.**

Clotrimazole / Betamethasone Cream Label

Packaged and
distributed by:



STAT RX USA

Gainesville,
GA 30501

**Betamethasone/Clotrimazole
Cream 15 g**

Generic For:

NDC 16590-033-15

Prod# 033-15
Lot# SAMPLE

Each Gram Contains: 10.0mg Clotrimazole USP/
0.64mg Betamethasone dipropionate (equivalent to
0.5mg Betamethasone) cream

Mfg By: Aclavis Mid Atlantic LLC
Lincolnton, NC 28092

NDC 0472-0379-15

Mfg Lot: SAMPLE

Discard After: 04/11

8W 10/15/2009 372276

RX ONLY-KEEP OUT OF REACH OF CHILDREN

Caution: Federal law prohibits transfer of this drug to any person other than the patient for whom it was prescribed.



16590-033-15

Dosage: See package insert
Store between 59-86 degrees F